REMARKS

Claims 17-33 are pending in this application. Claims 17, 19, 24, 26, 28, 32 and 33 have been amended as discussed below.

Claim Objections

Applicant thanks the Examiner for correctly renumbering the pending claims. The List of Claims reflects the corrected numbering.

Claim Rejections – 35 USC §112, second paragraph

The Examiner has rejected claims 17-33 under 35 USC §112, second paragraph, as being indefinite.

Claims 17 and 26

The Examiner rejected claims 17 and 26 for use of the term "DNase". The Examiner is concerned that the term "DNase" is unclear as there are several types of DNase from many different organisms.

Claims 17 and 26 have been amended to recite that the DNase is a human DNase. Support for this amendment can be found throughout the specification. For example, on page 10 under the heading Definitions, the specification sets forth that the term "DNase" or "human DNase" or "recombinant human DNase" or grammatical equivalents herein is meant a polypeptide having the amino acid sequence of human mature DNase as well as amino acid sequence variants thereof (including allelic variants) that are enzymatically active in hydrolyzing DNA. "DNase" includes both purified mixtures of deamidated and non-deamidated human DNase as well as purified forms of each. Furthermore, the Examples disclose studies of the effect of sugars on the thermally induced aggregation of human recombinant DNase.

Applicant asserts that amended claims 17 and 26 are in compliance with 35 USC §112, second paragraph.

Claims 17 and 18

The Examiner rejected claims 17 and 18 based on his opinion that it is not clear if the temperature step is required to minimize the aggregation or if the aggregation is minimized in spite of the elevated temperature.

Amended claim 17 recites a process for minimizing thermal aggregation of a human DNase in a liquid solution comprising introducing a DNase aggregation-inhibiting amount of sugar to a solution comprising DNase, wherein the temperature of said DNase solution is subsequently elevated to above 37°C and aggregation of DNase at said elevated temperature is reduced. Claim 18 specifies that the temperature of the solution is elevated above about 60°C.

Amended claim 17, and claim 18 dependent thereon, clearly specify that aggregation of DNase is a result of the elevation in the temperature of the solution. Additionally, the Applicant respectfully asserts that the specification is quite clear in demonstrating that the aggregation of DNase is reduced in spite of the elevated temperature. For example, under the Field of Invention heading on page 1, the invention is described as relating to the preparation of liquid solutions of DNase that are protected from thermally induced aggregation of the DNase. Similarly, on page 3 under the Summary of the Invention heading, the specification states that the invention is predicated upon the finding of an exceptional characteristic found attributable to a particular component which in liquid solution together with DNase protects the DNase from thermally induced aggregation. Further, on page 5, beginning at line 21, the specification states that the invention is directed to methods for the preparation of liquid solutions that minimize DNase aggregation brought about from thermal instability. Additionally, the Examples provide controls which show that DNase is aggregated at high temperatures. On page 11, under the heading Thermally Induced Aggregation, the specification provides data showing aggregation of DNase

as a function of the increase in temperature (Figure 1). Example 2 then proves that the methods and solutions of the invention can reduce the thermally induced aggregation of DNase.

Applicant submits that one of skill in the art would understand that claims 17 and 18 as amended are directed to the protection of the DNase solution from aggregation brought on by the elevation of the temperature to of the DNase solution above 37°C or above about 60°C. As such, claims 17 and 18 are not indefinite.

Claims 19-22 and 28-30

The Examiner rejected claims 19-22 and 28-30 based on his opinion that it is not clear if the DNase containing solutions have the recited pH values or if the pH values are those for intended use.

Applicant has amended claim 19 for clarity to recite a process according to claim 17, wherein the pH of said solution is below pH 7.0. Claim 19 thus specifies that the solution in claim 17 is at a pH of below pH 7.0 prior to the elevation of the temperature to above 37°C. This amendment finds support throughout the specification including at page 4, beginning at line 23, which sets forth that the invention relates to the stabilization of less than neutral pH liquid solutions containing DNase from precipitation. Additionally, Example 2 sets forth the use of sugars to minimize the thermal aggregation of DNase in a liquid solution where the solution is at a pH between 6 and 7.

Claim 19, and claims 20-22 dependent thereon, now recite that the pH of the solution is at or below a specific pH value.

Claim 28 has been amended for clarity to recite a DNase solution according to claim 26, wherein the pH of said solution is below 7.0. Amended claim 28, and claims 29-30, are not idefinite.

The amendments to the claims 19-22 and 28-30 serve to place the claims in compliance with 35 USC §112, second paragraph. Applicant requests withdrawal of the rejection.

Claim 32

The Examiner rejected claim 32 for reciting an improper Markush group. Claim 32 has been amended to place the claim in proper Markush form, thus addressing the Examiner's rejection. Claim 24 has also been similarly amended to correct the claim format.

Claim 33

The Examiner rejected claim 33 for lacking antecedent basis for the phrase "further comprises the steps of spray-drying" because the process is directed to a method of making a solution, not a solid. Claim 33 has been amended to recite a composition comprising the DNase solution according to claim 26, wherein said solution is further spray-dried to a respirable DNase-containing powder that is therapeutically effective when administered into the lung of an individual. The amendment serves to place claim 33 in compliance with 35 USC §112, second paragraph. Applicant requests withdrawal of the rejection.

Claim Rejections – 35 USC §102(b)

Heicke

The Examiner rejected claims17-19, 22-24, 26-28, and 31-33 as being anticipated by Heicke (1969).

The Examiner is relying the theory of inherent disclosure in this rejection. However, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP §2131. Heicke does not teach each and every element of the rejected claims.

Heicke is directed to the purification of a high molecular weight DNase from a marine sponge *Veronigia aerophoba.* The claims of the present invention, however, are directed toward a DNase having the amino acid sequence of human mature DNase. As pointed out by Heicke, on page 165, column 1, the marine sponge was chosen with the expectation that the DNase isolated

from the organism would have "unusual properties" as compared to previously characterized DNases from mammalian sources. Indeed, the DNase isolated by Heicke exhibited a much higher molecular weight than has been observed for mammalian DNases. Heicke found the molecular weight of the DNase from the marine sponge to be about 62,000 D or 65,000 D (depending on the method of determining the molecular weight) as compared to mammalian DNases which range from 17,000-38,000 D (rhDNase has a molecular weight of 29,250 D).

The claims of the present invention are directed toward a human DNase. Based on the molecular weight information provided by Heicke, the marine sponge DNase would not be expected to have the same amino acid sequence of human mature DNase. As such, Heicke does not recite each and every element of claims 17-19, 22-24, 26-28, and 31-33. Applicant respectfully requests withdrawal of the rejection.

Khouw

The Examiner rejected claims17-19, 22, 26-28, and 32-33 as being anticipated by Khouw (US 4,065,355).

The Examiner is relying the theory of inherent disclosure in this rejection. However, a claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference. MPEP §2131. Khouw does not teach each and every element of the rejected claims.

As with Heicke, the DNase disclosed in Khouw is not human DNase but rather bovine DNase. Khouw may speak broadly in terms of any DNase but Khouw does not teach a solution comprising a DNase aggregation-inhibiting amount of sugar and human DNase. Additionally, while Khouw discusses the use of sugars to elute the bovine DNase from a purification column, it does not disclose that the DNase remain in the sugar solution. In fact, the examples indicate that the DNase is immediately removed from the sugar solution via ammonium sulfate precipitation, desalting and lyophilization. This distinction is particularly relevant for claims17-19, and 22 which recite a process for minimizing thermal aggregation of DNase in a liquid

solution where the solution is subsequently elevated to above 37°C and aggregation of DNase at said elevated temperature is reduced. Khouw does not teach or suggest that the DNase eluted from the purification column be subjected to an elevation in temperature nor does it teach or suggest that the presence of the sugar component in the elution buffer would serve to keep the DNase in solution if the temperature of the solution was so elevated.

Karimov

The Examiner rejected claims17-18, 23-24, 26-27, and 31-33 as being anticipated by Karimov (1982). Applicant notes that the Examiner has not provided the Karimov reference. Applicant is basing this response on the abstract of this Russian language paper that was obtained via the public PAIR site.

Karimov discloses the use of 0.4M mannitol in a solution used to resuspend isolated plant protoplasts. The resuspended protoplasts are then digested with pancreatic DNase. While it is not set forth in the abstract, it is highly unlikely that Karimov used human DNase for this study. In the year of the study, 1982, one could not obtain recombinant human DNase and it is unlikely, if not impossible, that Karimov would have used pancreas from a human source to isolate the DNase for the study. As such, Karimov does not teach each and every element of the instant claims. Applicant requests withdrawal of this rejection absent a showing that the DNase disclosed in Karimov is a human DNase.

Claim Rejections – 35 USC §103(a)

The Examiner rejected the claims (presumably 17-33 as the identity of the claims under this rejection was not specified by the Examiner) as being anticipated by Heicke in view of Arakawa (1982), Back (1979), and van de Beek (1969). Applicant respectfully traverses this rejection.

As discussed above under the section entitled Claim Rejections – 35 USC §102(b), Heicke does not teach or suggest all of the elements of the pending claims which are directed toward a human DNase. Arakawa, Back, and van de Beek do not cure the deficiencies of Heicke.

The Examiner cites Arakawa as disclosing the use of sugars to stabilize the structure of proteins in general. Arakawa does not disclose studies using human DNase. Additionally, Arakawa does not teach or suggest a process for minimizing thermal aggregation of DNase in a liquid solution comprising introducing a DNase aggregation-inhibiting amount of sugar to a solution comprising DNase, wherein the temperature of said DNase solution is subsequently elevated to above 37°C and aggregation of DNase at said elevated temperature is reduced as set forth in amended claim 17. Nor does it teach a DNase solution comprising DNase and a DNase aggregation-inhibiting amount of sugar wherein said DNase solution is minimally aggregated when said solution is at a temperature greater than 37°C as set forth in amended claim 26. Arakawa provides studies of 6 proteins each showing varying levels of stabilization by sugars as measured by partial specific volumes. These measurements were carried out at 20 C. Thus, while Arakawa provides a general observation that the presence of sugar in a solution with a protein may result in stabilization of the protein at 20 C, it does not teach that thermally induced aggregation of human DNase can be reduced by including sugar in the solution with the human DNase.

The Examiner also cites Back as disclosing the use of sugars to stabilize the structure of proteins in general. Back does not disclose studies using human DNase. Back provides a

general observation that the presence of sugar in a solution with a protein may result in stabilization of the protein even as the temperature of the solution is raised. However, Back does not teach that thermally induced aggregation of human DNase, can be reduced by including sugar in the solution.

The Examiner cites van de Beek as disclosing the use of sugars to preserve the activity of proteins in general during spray-drying. Van de Beek does not disclose studies using human DNase. Additionally, van de Beek does not teach or suggest a process for minimizing thermal aggregation of DNase in a liquid solution comprising introducing a DNase aggregation-inhibiting amount of sugar to a solution comprising DNase, wherein the temperature of said DNase solution is subsequently elevated to above 37°C and aggregation of DNase at said elevated temperature is reduced as set forth in amended claim 17. Nor does it teach a DNase solution comprising DNase and a DNase aggregation-inhibiting amount of sugar wherein said DNase solution is minimally aggregated when said solution is at a temperature greater than 37°C as set forth in amended claim 26. Van de Beek discloses that the addition of sugars to a composition comprising the enzyme rennin results in recovery of more enzyme activity after spray-drying of the composition. Thus, while van de Beek provides a general observation that the presence of sugar in a solution with a protein may result in stabilization of the enzyme during the spray-drying process, it does not teach that thermally induced aggregation of a specific protein, human DNase, can be reduced by including sugar in the solution with the human DNase.

CONCLUSION

Applicants submit that the claims are now in condition for allowance and early notification to that effect is respectfully requested. Please direct any calls in connection with this application to the undersigned at (415) 781-1989.

Respectfully submitted,
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